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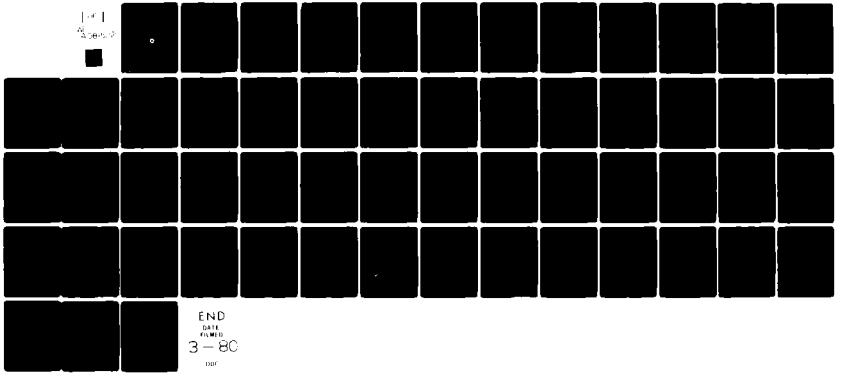

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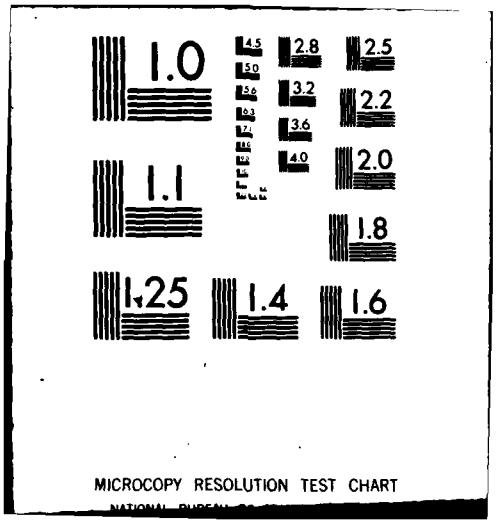
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MODELLING DIFFERENTIAL EXPOSURE AND DIFFERENTIAL SENSITIVITY CHARACTERISTICS IN NON-MELANOMA SKIN CANCER INCIDENCE

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(Institute for Defense Analyses Paper P-1422)

Pythagoras Cutchis

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Prepared for

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16. Abstract

A mathematical non-melanoma skin cancer incidence model is derived which includes the effects of differential exposure and differential sensitivity in the white population of a given geographic region. These effects, and their variations with geographic region, are shown to be fundamental to an understanding of the behavior of skin cancer incidence as it exists today and as it would be predicted to increase in the event of a decrease in stratospheric ozone. The model is applied to available New York City data to determine the representation in the population of nine postulated exposure-sensitivity groups. The effects of changes in exposure and sensitivity parameters on incidence are illustrated by comparing New York City with a hypothetical rural region at the same latitude. The effect of not eliminating non-solar-related skin cancers in skin cancer incidence data on the prediction of increased incidence due to stratospheric ozone reduction is found to introduce an error which may be positive or negative. Programs which should be pursued in order to effectively utilize the mathematical model are recommended. Areas requiring urgent attention include UV-B instrumentation, skin cancer pathology, skin cancer data collection and classification, and population exposure surveys.

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FOREWORD

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The author is indebted to the following individuals for their critical reviews of this paper: Dr. Anita Baker-Blocker, Assistant Professor of Environmental Health, School of Public Health, University of Illinois; Dr. Thomas P. Nigra, Chairman, Dermatology Section, Washington Hospital Center; and Dr. Robert C. Oliver of the Institute for Defense Analyses. The document as it stands is the responsibility of the author. Comments and criticism are invited.

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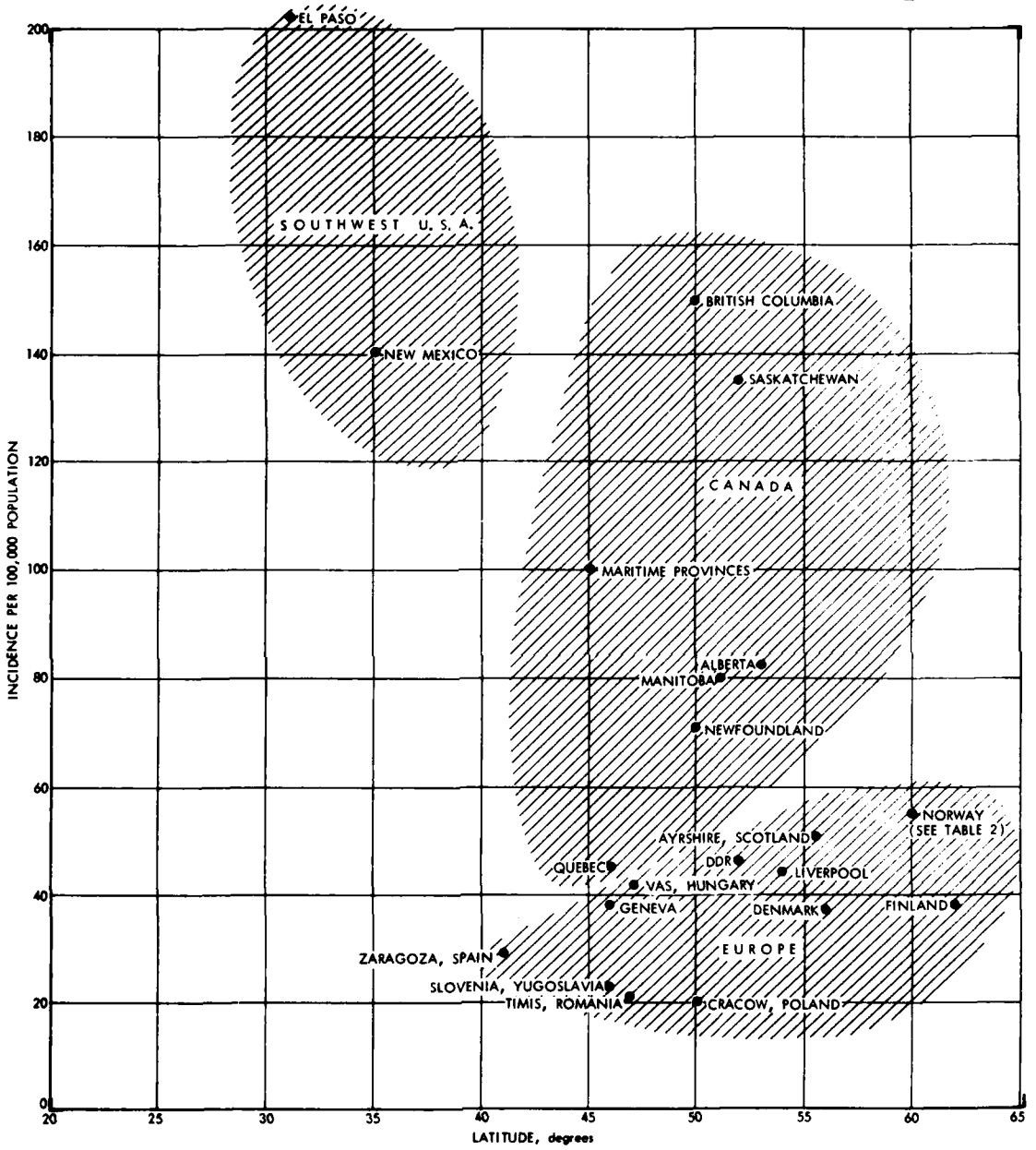
I. INTRODUCTION

Non-melanoma skin cancer incidence in a given geographic region is today recognized as being strongly related to the intensity of the solar ultraviolet radiation received, which is highest near the equator. Thus, if skin cancer incidence is plotted as a function of latitude, it would be expected that there would be a well-defined latitude gradient. In Fig. 1 is reproduced a plot of non-melanoma skin cancer incidence for male white populations between 30° and 60° north latitude (Ref. 1). While there is a discernible latitude gradient in this plot, there is a very large scatter between 40° and 55° which can be principally attributed to the combined effects of poor data, differences in climate, differences in ozone thickness, differences in sun exposure habits of the population (which are related to climate), and differences in population sensitivity to non-melanoma skin cancer. The complex ways in which the latter two effects influence skin cancer incidence are explored in this paper. A simplified exposure-sensitivity model is derived and applied to available data for New York City. A comparison is then made with a hypothetical rural region of the same latitude, in which exposure and sensitivity parameters can be expected to differ widely.

Nearly all of the non-melanoma skin cancer incidence models that have been proposed for predicting the increase in incidence resulting from an increase in solar ultraviolet radiation due to



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon (IARC Scientific Publications No. 15) 1976.

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FIGURE 1. Non-melanoma skin cancer, age-standardized incidence for white males.

a postulated decrease in stratospheric ozone are aggregate models, i.e., it is implicitly assumed that all members of a given white population are exposed to the same amount of UV-B solar radiation (e.g., some fraction of the mean UV-B radiation incident on the ground) and have the same sensitivity to skin cancer. In actuality, of course, there are very wide differences in both the sun exposure habits and sensitivity of individuals. Consequently, it can be expected that individuals who seldom expose themselves to the sun and who have low sensitivity to skin cancer would be less affected by a postulated decrease in the amount of stratospheric ozone than those individuals who have high sensitivity and high sun exposure. However, if this high-exposure, high-sensitivity group constitutes but a small fraction of the overall population, its contribution to the value of skin cancer incidence for the whole population could be small. It also follows that any additional cases to be expected from this high risk group as a result of a postualted decrease in stratospheric ozone could constitute but a small fraction of the total additional cases. In the model derived below, skin cancer incidence is derived as a function of the probability distributions of exposure and sensitivity in the population. To adequately describe these distributions, it is necessary to assume ranges of relative exposure and sensitivity values and the probability functions within these assumed ranges. The model indicates that the skin cancer incidence following any calculated change in the ozone column, e.g., based on 2-D modelling of the effects of aircraft effluents, will depend significantly on the differential sensitivity and exposure characteristics of the population residing in a given geographic region, as well as on the magnitude of the change in the ozone column.

II. MODEL FOR SKIN CANCER INCIDENCE

Non-melanoma skin cancer incidence increases very rapidly with age. When plotted on semi-log paper, age-specific non-melanoma skin cancer incidence typically approximates a straight line, as indicated by the diverse smoothed data in Fig. 2 for incidence in Finland, Sweden, Japan (Ref. 2) and mortality in the U.S. (Ref. 3). The slopes of the smoothed lines are almost equal; their values indicate an incidence doubling time of 6 to 7 years. For a population group of age A, exposure E, and sensitivity S, the incidence I′ can therefore be represented approximately by

$$I'(A, S, E) = k\, f(S, E)\, e^{\lambda A}, \qquad (1)$$

where k and λ are constants.

The term "exposure," here designated by E, represents the received biologically weighted UV-B (sometimes referred to as DUV or damaging UV) flux integrated over exposure time. It is assumed here that the biological weighting function (usually assumed to be the erythema action spectrum) has the same shape for all individuals. However, Caucasians are known to differ in their tendency to develop solar-related skin cancer because of differences in the UV reflectance and absorption properties of the human skin and differences in DNA repair mechanisms; this complex biological difference is covered by the sensitivity factor S.

The function f (S, E) is assumed to follow the power law

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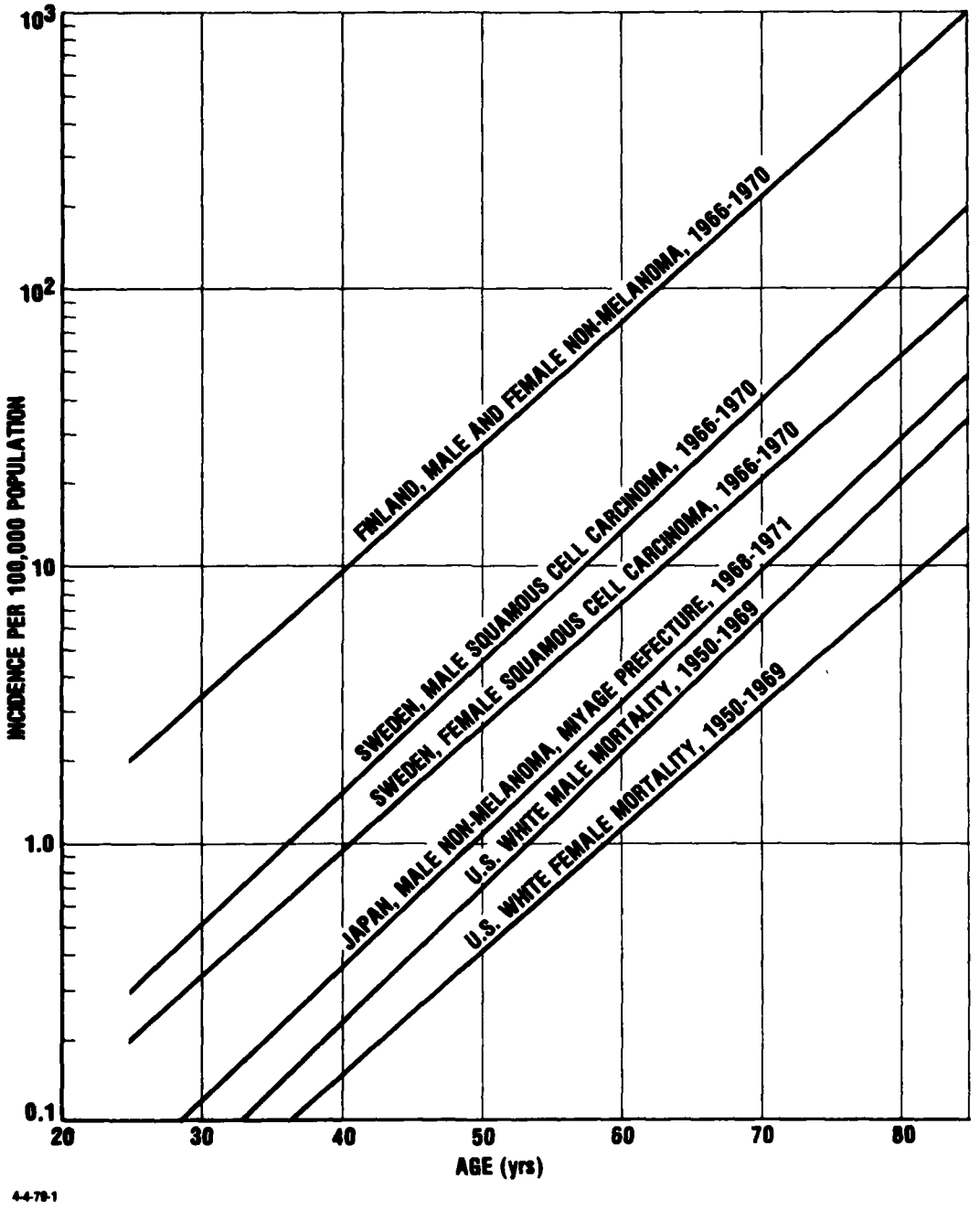

FIGURE 2. Non-melanoma skin cancer incidence and mortality vs age (heavily smoothed).

$$f\,(S, E) = (SE)^n = D^n \quad . \tag{2}$$

The product SE in Eq. (2) is a measure of the carcinogenically effective received ultraviolet dose D for a population of exposure E and sensitivity S, and n is the biological amplification factor, i.e.,

$$n = \frac{dI/I}{dD/D} \quad . \tag{3}$$

n is apparently independent of age A, since the distance between any two lines for two different received dose levels in Fig. 2 is essentially a constant. The higher the value of n, of course, the higher is the percentage increase in skin cancer incidence for a specified percentage increase in UV dose.

If p(A), p(E), and p(S) represent the probability density functions for population age, exposure, and sensitivity, respectively, incidence I for the whole population of a given region is given by

$$I = k \int_A \int_E \int_S (SE)^n \, e^{\lambda A} \, p(S)p_S(E)p(A)dSdEdA \tag{4}$$

$$= k' \int_E \int_S (SE)^n \, p(S)p_S(E)dSdE, \tag{5}$$

where $p_S(E)$ is the conditional probability of exposure E given a sensitivity S, and k′ is a constant.

In order to reduce the triple integral (4) to a double integral (5) by integrating over age, it was implicitly assumed that p(S) and $p_S(E)$ are independent of age. For a stable population composition such as that to be found in Sweden, p(S) indeed should be close to being independent of age. However, $p_S(E)$ for adults could be expected to be dependent on age as

well as sensitivity. Older retired people who are healthy probably spend more time outdoors than they did when working, while the infirm probably spend less time outdoors. While these effects tend to offset each other, the extent to which they do not represents a deficiency in this representation.

The continuous probability distributions in Eq. (5) are unknown quantities at the present time. It is easier to work with a simplified discrete form of Eq. (5), i.e.,

$$I = k' \sum_{i=1}^{i=a} \sum_{j=1}^{j=b} (E_i \, S_j)^n \, p_{ij} \, , \qquad (6)$$

where each population subgroup of exposure E_i and sensitivity S_j has a probability p_{ij} of being represented in the total population. The latter is divided into "a" exposure subgroups and "b" sensitivity subgroups, and

$$\sum_{i=1}^{i=a} \sum_{j-1}^{j=b} p_{ij} = 1 \quad .$$

III. ANALYSIS OF SKIN CANCER INCIDENCE IN NEW YORK CITY

Very little quantitative information is available in the literature comparing incidences of population subgroups of different exposures and sensitivities in a given geographical region. The only quantitative information of this kind known to the author is for a basal cell epithelioma control study for New York City (Ref. 4). The data in this study fortuitously provides values for some of the exposure and sensitivity parameters required in the analysis below. It should be noted that while the bulk of non-melanoma skin cancers are basal cell epitheliomas, squamous cell carcinomas constitute a sizeable fraction of all skin cancers. Moreover, not all basal cell epitheliomas are induced by solar ultraviolet radiation (Ref. 1).

Gellin et al. (Ref. 4) divided the population into three exposure subgroups, according to the estimated daily hours of outdoor activity. The low-exposure subgroup spent 0 to 2 hours daily outdoors, the moderate-exposure group 3 to 5 hours, and the high-exposure group 6 or more hours. The percentage distribution of these subgroup populations in the BCE (basal cell epithelioma) and control groups are given in Table 1 (Ref. 4). The data set used consisted of 759 cases of basal cell epithelioma and 757 controls, and was restricted to Caucasians.

TABLE 1. PERCENTAGE DISTRIBUTION BY ESTIMATED DAILY HOURS OF OUTDOOR ACTIVITY

EXPOSURE (hrs)	BCE	CONTROLS
0-2	24.7	65.0
3-5	46.4	25.1
6+	28.9	9.9

Information on a highly sensitive subgroup characterized by light hair, fair complexion, and light eyes was also reported, independent of exposure, and for that portion of this particular subgroup that estimated an outdoor exposure of 6 or more hours daily. The percentage distributions are given in Table 2 for the BCE and control groups (Ref. 4).

TABLE 2. PERCENTAGE DISTRIBUTION FOR HIGHLY SENSITIVE SUBGROUPS

SUBGROUPS	BCE	CONTROLS
Highly Sensitive	15.3	4.2
Highly Sensitive and 6+ Hrs. Outdoor Activity	5.3	0.6

An inspection of Tables 1 and 2 reveals the significance of outdoor exposure on skin cancer incidence, particularly for those who are highly sensitive.

The New York City population is assumed to be divided into the three exposure groups: E_1, E_2, and E_3, as indicated in Table 1, and three sensitivity groups: S_1, S_2, and S_3. The subscript 1 denotes a low, 2 a moderate, and 3 a high value of exposure or sensitivity. Consequently, there will be 3 x 3 or nine sensitivity-exposure groups, each characterized by a dose $(E_i\ S_j)^n$ as indicated in the matrix of Fig. 3 for n = 1.

SENSITIVITY	EXPOSURE E_1	E_2	E_3
S_1	E_1S_1	E_2S_1	E_3S_1
S_2	E_1S_2	E_2S_2	E_2S_2
S_3	E_1S_3	E_2S_3	E_3S_3

FIGURE 3. DOSE MATRIX (n=1)

For each of the population subgroups in Fig. 3 characterized by dose E_i S_j, there is associated a probability p_{ij}, as indicated by the probability distribution matrix of Fig. 4. The probability p_{ij} may be interpreted as either the probability of finding a randomly chosen member of the whole population who has exposure E_i and sensitivity S_j, or the fraction of the whole population who have exposure E_i and sensitivity S_j.

SENSITIVITY \ EXPOSURE	E_1	E_2	E_3
S_i	p_{11}	p_{21}	p_{31}
S_2	p_{12}	p_{22}	p_{32}
S_3	p_{13}	p_{23}	p_{33}

FIGURE 4. PROBABILITY DISTRIBUTION MATRIX

From Table 1 and Fig. 4 it follows that

$$p_{11} + p_{12} + p_{13} = 0.65 \tag{7}$$

$$p_{21} + p_{22} + p_{23} = 0.25 \tag{8}$$

$$p_{31} + p_{32} + p_{33} = 0.10 \tag{9}$$

If f_1, f_2, and f_3 represent the fractions of the New York City population with sensitivities S_1, S_2, and S_3 respectively, then from Fig. 4

$$p_{11} + p_{21} + p_{31} = f_1 \tag{10}$$

$$p_{12} + p_{22} + p_{32} = f_2 \tag{11}$$

$$p_{13} + p_{23} + p_{33} = f_3 = 1-f_1-f_2 \tag{12}$$

since the f_i values are subject to the constraint

$$\sum_{i=1}^{i=3} f_i = 1 \qquad (13)$$

Eq. (12) is not an independent equation since it can be derived from Eqs. (7), (8), (9), (10), and (11).

From Eq. (6), Table 1, Fig. 1, and Fig. 3 it follows that the ratio of the contribution to BCE incidence from the moderate exposure group (column 2 of each matrix) to the contribution from the low exposure group (column 1 of each matrix) is given by

$$\frac{E_2 S_1 p_{11} + E_2 S_2 p_{22} + E_2 S_3 p_{23}}{E_1 S_1 p_{11} + E_1 S_2 p_{12} + E_1 S_3 p_{13}} = \frac{46.4}{24.7} \qquad (14)$$

$$= 1.88$$

and that the ratio of the contribution to BCE incidence from the high exposure group (column 3 of each matrix) to the contribution from the low exposure group is given by

$$\frac{E_3 S_1 p_{31} + E_3 S_2 p_{32} + E_3 S_3 p_{33}}{E_1 S_1 p_{11} + E_1 S_2 p_{12} + E_1 S_3 p_{13}} = \frac{28.9}{24.7} \qquad (15)$$

$$= 1.17$$

From Table 2 and Fig. 4 it can be seen that the ratio of the percentage of New York City people who are in the highly sensitive group to the percentage that are highly sensitive and spend 6 or more hours daily outdoors is given by

$$\frac{p_{13} + p_{23} + p_{33}}{p_{33}} = \frac{4.2}{0.6} = 7.0 \qquad (16)$$

or

$$p_{13} + p_{23} - 6.0\, p_{33} = 0 \quad . \qquad (17)$$

From Table 2, Eq. (6), Fig. 3, and Fig. 4 it can be seen that the ratio of the percentage of BCE cases in the highly sensitive group to the percentage of BCE cases in the highly sensitive group who also spend 6 or more hours daily outdoors is given by

$$\frac{E_1 S_3 p_{13} + E_2 S_3 p_{23} + E_3 S_3 p_{33}}{E_3 S_3 p_{33}} = \frac{15.3}{5.3} \qquad (18)$$

or

$$E_1 p_{13} + E_2 p_{23} - 1.887\, E_3 p_{33} = 0 \quad . \qquad (19)$$

If values for f_1, f_2, E_1, E_2, E_3, S_1, S_2, and S_3 are assigned, it is possible to solve the nine independent linear equations 7, 8, 9, 10, 11, 14, 15, 17, and 19 for the nine p_{ij} values. Since only relative values of exposure and sensitivity are necessary inputs to the solution, it is convenient to assign a value of unity for the low exposure and sensitivity groups, i.e.,

$$E_1 = 1 \qquad (20)$$

$$S_1 = 1 \qquad (21)$$

The remaining two values of group exposure and sensitivity, by definition, must satisfy the inequalities

$$1 < E_2 < E_3 \qquad (22)$$

$$1 < S_2 < S_3 \quad . \qquad (23)$$

The values of E_3 and S_3 determine the range of exposure and sensitivity. Unfortunately, there is no quantitative information available on sensitivity variations within white populations. There is some guidance for the selection of E values in the numerical values of estimated daily hours of exposure in Table 1. However, there are the following difficulties in selecting appropriate E values for group exposure:

1. The low exposure group spends 0 to 2 hours outdoors daily, and it is tempting to take a mean value of one hour as representative of this group, but the distribution within this 2-hour period is unknown; the time mean could lie significantly below or above the 1-hour value.

2. Time spent outdoors is not a very good measure of the received solar ultraviolet dose, but it is the only data available. Exposures during the hours 10:00 AM to 2:00 PM, of course, result in much higher UV doses than early morning or late afternoon exposures of equal duration. Summer exposures also result in higher UV doses than exposures during the other seasons for the same time period.

There exists an acceptability constraint on the set of the input values E_2, E_3, S_2, S_3, f_1, and f_2 that are selected: the solution of the simultaneous equations must result in a set of nine positive p_{ij} values, i.e., a negative value of probability has no physical meaning.

Parameter values are listed in Table 3 for 22 cases which were selected for solution by a computer. Of these, seven cases were found to result in a solution with all nine p_{ij} values positive (✓); the remaining 15 cases resulted in one or more negative values (X) of p_{ij} and hence are unacceptable.

TABLE 3. ACCEPTABILITY OF CASES INVESTIGATED

Case	n	E_2	E_3	S_2	S_3	f_1	f_2	Acceptability
A	1	4	8	2	4	0.2	0.6	✓
B	1	4	8	2	4	0.1	0.8	X
C	1	4	8	2	4	0.3	0.4	X
D	1	4	8	2	3	0.2	0.6	✓
E	1	4	8	2	3	0.1	0.8	X
F	1	4	8	2	3	0.3	0.4	X
G	1	4	8	3	9	0.2	0.6	✓
H	1	4	8	3	9	0.1	0.8	✓
I	1	4	8	3	9	0.3	0.4	X
J	1	4	8	3	9	0.5	0.3	X
K	1	4	8	3	9	0.2	0.3	X
L	1	4	6	2	4	0.2	0.6	X
M	1	4	6	2	4	0.1	0.8	X
N	1	4	6	2	4	0.3	0.4	✓
O	1	4	6	2	4	0.4	0.2	✓
P	1	4	6	3	6	0.2	0.6	X
Q	1	4	6	3	6	0.1	0.8	X
R	1	4	6	3	6	0.3	0.4	X
S	2	4	8	2	3	0.2	0.6	X
T	2	4	8	2	3	0.1	0.8	X
U	2	4	8	2	3	0.3	0.4	X
V	2	4	8	2	3	0.15	0.7	✓

The p_{ij} matrices for the seven acceptable cases listed in Table 3 are given in Fig. 5. All cases except the last four assumed a linear dose-response relationship, i.e., n = 1. All cases except unacceptable cases J and K assumed a symmetric distribution of sensitivity in the population, i.e., $f_1 = f_3$ or $f_2 = 1 - 2 f_1$. For each of five sets of exposure and sensitivity values, the case $f_1 = 0.2$ was assumed, and additional cases below and above this value were investigated to determine how sensitive the solution was to this parameter. If all the parameters except f_1 are held constant, each p_{ij} is a linear function of f_1, as illustrated in Fig. 6, which encompasses cases A, B, and C. Note that in order for all p_{ij} values to be positive, the particular conditions cited in Fig. 5 require that $0.134 < f_1 < 0.240$.

The seven acceptable solutions in Table 3 can not all be correct; indeed, it cannot be expected that any one of these solutions could be correct for the following principal reasons:

1. The set of cases investigated is only a small fraction of the possible number of sets that could be obtained by taking different combinations of the assumed parameter values in Table 3 and by considering additional parameter values.

2. The model is extremely crude, e.g., the assumption of three exposure and three sensitivity groups is a gross simplification of the physical situation involving continuous distributions in both exposure and sensitivity.

3. The input incidence data for New York City is crude, since it is based on a total of only 759 BCE cases in the period January 1955 to March 1959 (Ref. 4).

4. New York City has a polyglot population with a large fraction of immigrants who experienced a different UV environment in their native lands. Non-melanoma skin cancer incidence is a function of lifetime UV dose (Ref.5).

A

.1085	.0335	.0581
.4567	.1299	.0134
.0848	.0866	.0286

B

.1471	.0053	.0476
.4183	.1579	.0238
.0846	.0869	.0286

C

.0532	.0831	.0638
.5123	.0801	.0076
.0846	.0869	.0286

H

.0500	.0109	.0390
.5577	.1956	.0467
.0423	.0434	.0143

N

.2803	.0033	.0163
.1888	.1704	.0408
.1809	.0763	.0429

O

.3408	.0260	.0332
.0680	.1223	.0097
.2411	.1017	.0571

V

.0119	.1230	.0152
.5882	.0484	.0635
.0500	.0787	.0215

FIGURE 5. PROBABILITY MATRICES FOR SEVEN ACCEPTABLE CASES

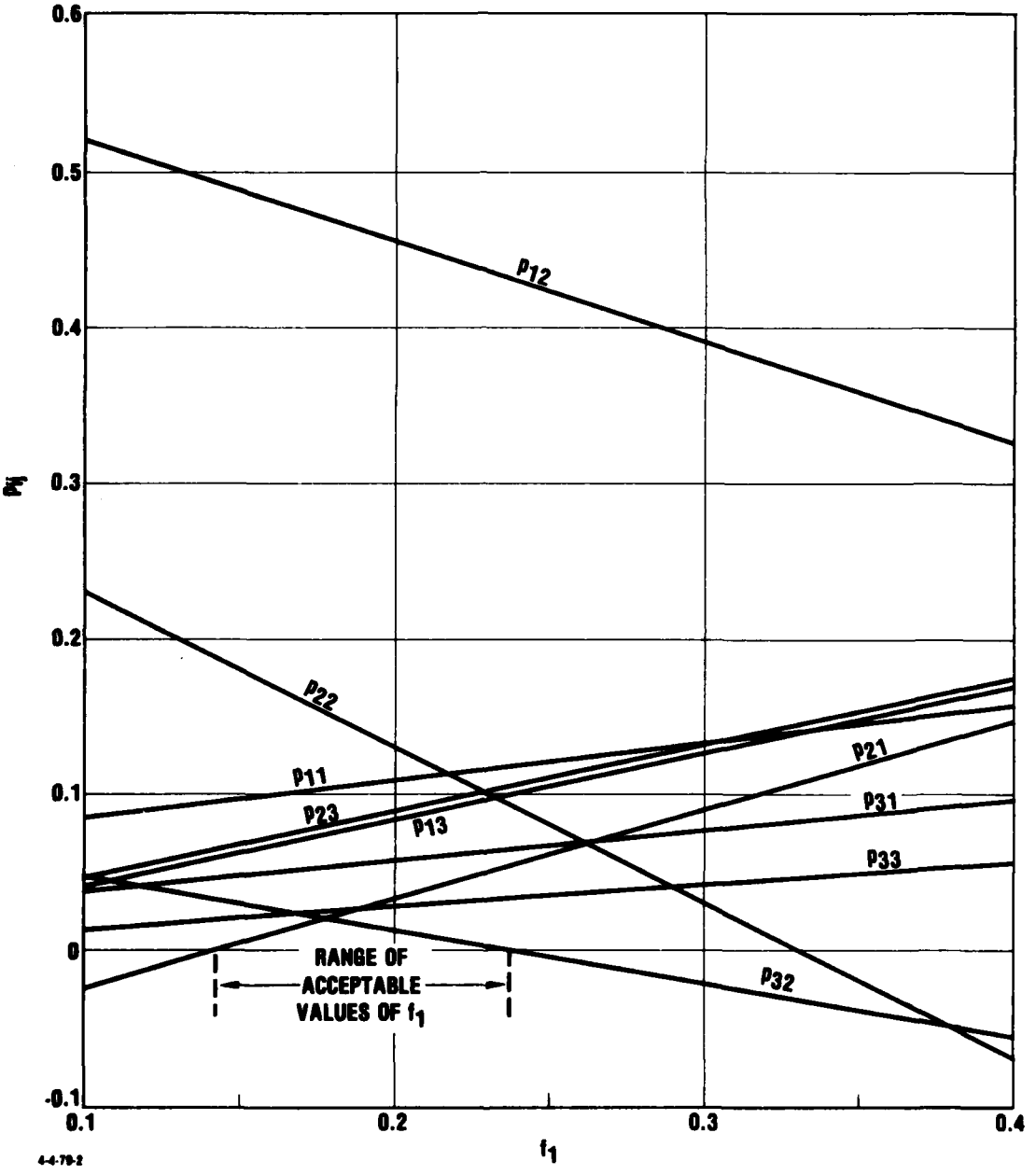

FIGURE 6. Population probabilities p_{ij} for $f_1 = f_3$, $n = 1$, $E_2 = 4$, $E_3 = 8$, $S_2 = 2$, and $S_3 = 4$

5. The input incidence data used for New York City was for the combined sexes. Exposure behavior and clothing, and consequently incidence, vary significantly with sex.

6. Perhaps as many as one-half of basal cell carcinomas are not induced by solar ultraviolet radiation in northern U.S. cities (Ref. 1).

7. Squamous cell carcinomas were not included.

8. Differences in exposure with age were not considered. Any future models including age as a parameter will require three-dimensional matrices.

It was deemed not worthwhile to investigate additional cases in response to the first reason cited above because of the limitations imposed by the other reasons. It is possible, however, to devise criteria which enable comparisons to be made between the seven acceptable solutions in order to select the solution that best fits the incidence data.

In Table 4 the probability ratios are given for groups of equal sensitivity and different exposure. Thus, for example, the ratio p_{11}/p_{21} is the ratio of the fraction of the least sensitive population which spends 0 to 2 hours daily outdoors to the fraction which spends 3 to 5 hours daily outdoors. For the entire population, the ratio of the fraction spending 0 to 2 hours daily outdoors to that spending 3 to 5 daily outdoors is 0.65/0.25 (Table 1) or 2.6.

One would expect that the ratio of time spent outdoors for the sensitive group to be greater, but not very much greater, than the ratio for the entire population. The ratio of 3.2 for Case A in Table 4 fulfills this expectation. Similarly, the ratio p_{21}/p_{31} for the fraction of the least sensitive group which spends 3 to 5 hours outdoors daily to the fraction spending more than 6 hours outdoors daily would not be expected to deviate

TABLE 4. PROBABILITY RATIOS FOR GROUPS OF EQUAL SENSITIVITY AND DIFFERENT EXPOSURE

CASE	P_{11}/P_{21}	P_{21}/P_{31}	P_{12}/P_{22}	P_{22}/P_{32}	P_{13}/P_{23}	P_{23}/P_{33}	Max.Ratio / Min.Ratio
A	3.2	0.6	3.5	9.7	1.0	3.0	16
D	27.8	0.1	2.6	6.6	1.0	3.0	278
G	0.6	1.3	6.4	10.5	1.0	3.0	18
H	4.6	0.3	2.9	4.2	1.0	3.0	15
N	84.9	0.2	1.1	4.2	2.4	1.8	425
O	13.1	0.8	0.6	12.6	2.4	1.8	16
V	0.1	8.1	12.2	0.8	0.6	3.7	122

greatly from 0.25/0.10 (Table 1) or 2.5. The ratio of 0.6 for Case A in Table 4 is one-fourth of that for the entire population, which seems unlikely but is not impossible since the least sensitive group would be more likely to seek high exposure than the population as a whole.

The second and third columns in Table 4 are the ratios for the moderate sensitivity group, and the fifth and sixth columns are the ratios for the high sensitivity group. Thus, for a given case, there are six ratios to be compared, and all six ratios would not be expected to deviate greatly from a value of 2.5.

As a measure of the spread in the values of the ratios for a given case, the maximum value is divided by the minimum value (last column in Table 4). A large max ratio/min ratio value indicates a large excursion from expected behavior. This value fell in the range of 15 to 18 for Cases A, G, H, and O, but exceeded 120 for Cases D, N, and V. The latter three cases represent too large a departure from expected behavior and are therefore discarded.

In Table 5, the probability ratios are given for groups of equal exposure and different sensitivity weighted by the appropriate f ratio. Only the four remaining Cases A, G, H, and O are considered. If $f_1 = f_2$, the ratio p_{11}/p_{12} would represent the ratio of the fraction of the low exposure population group of low sensitivity to the fraction of the low exposure group of moderate sensitivity. Since, in the cases investigated, $f_1 \neq f_2$, the ratio p_{11}/p_{12} is multiplied by f_2/f_1. If exposure were independent of sensitivity, it would be expected that $p_{11}/p_{12} \times f_2/f_1$ would be equal to unity. Values in Table 5 which deviate greatly from unity are considered less likely to be realistic than values which are close to unity.

By again applying the max ratio/min ratio criterion to the four cases in Table 5, a minimum value of 15 is obtained for Case H, and a maximum value of 50 for Case G. Thus, the H set

TABLE 5. PROBABILITY RATIOS FOR GROUPS OF EQUAL EXPOSURE AND DIFFERENT SENSITIVITY

CASE	$\frac{p_{11}}{p_{12}}\frac{f_2}{f_1}$	$\frac{p_{13}}{p_{12}}\frac{f_2}{f_3}$	$\frac{p_{21}}{p_{22}}\frac{f_2}{f_1}$	$\frac{p_{23}}{p_{22}}\frac{f_2}{f_3}$	$\frac{p_{31}}{p_{32}}\frac{f_2}{f_1}$	$\frac{p_{33}}{p_{32}}\frac{f_2}{f_3}$	Max Ratio / Min Ratio
A	0.71	0.56	0.77	2.00	12.99	6.40	23
G	0.31	0.50	3.11	3.25	25.18	11.29	50
H	0.72	0.61	0.45	1.78	6.68	2.45	15
O	2.51	1.77	0.11	0.42	1.71	2.94	27

of input values n = 1, $E_2 = 4$, $E_3 = 8$, $S_2 = 3$, $S_3 = 9$, and $f_1 = f_3 = 0.1$ appears to best fit the input New York City data if the population is divided into nine discrete sensitivity-exposure groups and the linear dose-response relationship is assumed to be valid. The fact that an acceptable but non-competitive solution was found for n = 2 (Case V in Table 3) indicates that there is a possiblity that a biological amplification factor n other than unity could lead to a better fit of the data.

The fraction I_{ij} of the total skin cancer incidence contributed by a group with exposure E_i and sensitivity S_j is given by

$$I_{ij} = \frac{E_i \, S_j \, p_{ij}}{\sum_{i=1}^{i=3} \sum_{j=1}^{j=3} E_i \, S_j \, p_{ij}} \quad . \tag{24}$$

In Fig. 7, the elements of the dose ($E_i \, S_j$), probability (p_{ij}), and incidence (I_{ij}) matrices are given for Case H. From the incidence fraction matrix it is seen that while only 1.4 percent of the population is in the high exposure-high sensitivity group, 12.1 percent of skin cancer cases occur in this group. On the other hand, whereas 5 percent of the population is in the low exposure-low sensitivity group, only 0.6 percent of the skin cancer cases occur in that group. These results are consistent with the fact that a high exposure-high sensitivity resident runs a risk of skin cancer 72 times higher than a low exposure-low sensitivity resident, as indicated by the dose matrix in Fig. 7, i.e., 12.1/1.4 ÷ .006/.05 = 72. While a majority of the population (55.8 percent) lies in the low exposure-moderate sensitivity group, only 19.6 percent of the skin cancer cases are found in this group. The group contributing most skin cancers is the moderate exposure-moderate sensitivity group, with

S_j \ E_i	1	4	8
1	1	4	8
3	3	12	24
9	9	36	72

DOSE (E_i S_j)

S_j \ E_i	1	4	8	$\sum_{i=1}^{i=3} p_{ij}$
1	.0500	.0109	.0390	.10
3	.5577	.1956	.0467	.80
9	.0423	.0434	.0143	.10
$\sum_{j=1}^{j=3} p_{ij}$	.65	.25	.10	

PROBABILITY (p_{ij})

S_j \ E_i	1	4	8	$\sum_{i=1}^{i=3} I_{ij}$
1	.0059	.0051	.0366	.0476
3	.1964	.2755	.1316	.6035
9	.0447	.1834	.1209	.3490
$\sum_{j=1}^{j=3} I_{ij}$	.2470	.4640	.2891	

$$\sum_{i=1}^{i=3}\sum_{j=1}^{j=3} E_j S_j p_{ij} = 8.5194$$

INCIDENCE FRACTION (I_{ij})

FIGURE 7. DOSE, PROBABILITY, AND INCIDENCE MATRICES FOR CASE H

27.6 percent compared to a population representation of 19.6 percent. Both the high exposure-low sensitivity group and the low exposure-high sensitivity group contribute approximately 4 percent to skin cancer incidence and have approximately the same 4 percent population representation.

As shown in the incidence fraction matrix of Fig. 7, addition of each element in a row yields the incidence fraction for a group of given sensitivity, and addition of each element in a column yields the incidence fraction for a group of given exposure. In Table 6, the population and incidence percentages are compared for the three assumed levels of exposure and sensitivity, i.e., low, moderate, and high. Residents with high exposure or high sensitivity contribute to incidence at a rate approximately triple that of their representation in the population. Residents with low exposure or low sensitivity contribute at a rate less than half their representation in the population. Residents of moderate exposure contribute at a rate almost double their population representation, while those of moderate sensitivity contribute at a rate approximately three-fourths of their population representation. Residents with high exposure or high sensitivity contribute at a rate three times higher than their representation in the population.

TABLE 6. POPULATION AND INCIDENCE PERCENTAGES FOR NEW YORK CITY

	EXPOSURE		SENSITIVITY	
LEVEL	POPULATION	INCIDENCE	POPULATION	INCIDENCE
Low	65	24.7	10	4.8
Moderate	25	46.4	80	60.3
High	10	28.9	10	34.9

The I_{ij} values in Fig. 7 also give information on the sources of new skin cancer cases in the event of a reduction in the amount of stratospheric ozone. The number of new cases would be found to have an exposure-sensitivity distribution that would parallel the I_{ij} distribution, i.e., each I_{ij} would receive the same percentage increase and hence any two elements of a matrix of number of new skin cancer cases would have the same ratio as their I_{ij} ratio.

IV. RURAL CASE

It is interesting to investigate the change in the elements of the incidence matrix in Fig. 7 if a hypothetical rural region were to be considered instead of New York City. In a region such as Iowa, which lies at approximately the same latitude as New York City and where farming is the predominant occupation, it might be expected that a majority of the population spends more than 6 hours outdoors daily* instead of the 10 percent for New York City.

In the hypothetical rural example of Fig. 8, the fraction of the population spending 6 or more hours outdoors daily is assumed to be 65 percent and the fraction spending 0 to 2 hours outdoors daily is assumed to be 10 percent, or the reverse of the New York City exposure distribution. The sensitivity distribution is assumed to be the same as that for New York City, i.e., $f_1 = 0.1$ and $f_2 = 0.8$. The moderate sensitivity-high exposure group was assumed to constitute 55 percent of the population, a value which corresponds to that of the moderate sensitivity-low exposure group in New York City. In this rural example, 83 percent of the skin cancers are in the high exposure group. A comparison of the population and incidence percentages for this hypothetical rural case is given in Table 7. Note in Table 7 that the high sensitivity group accounts for only 21 percent of the incidence whereas in Table 6 it accounted for 35 percent. The explanation for this surprising result is the

*Not likely to be true for the female population, but consideration of the sex difference is not required for purposes of comparison of this hypothetical rural case with the data set of Section III.

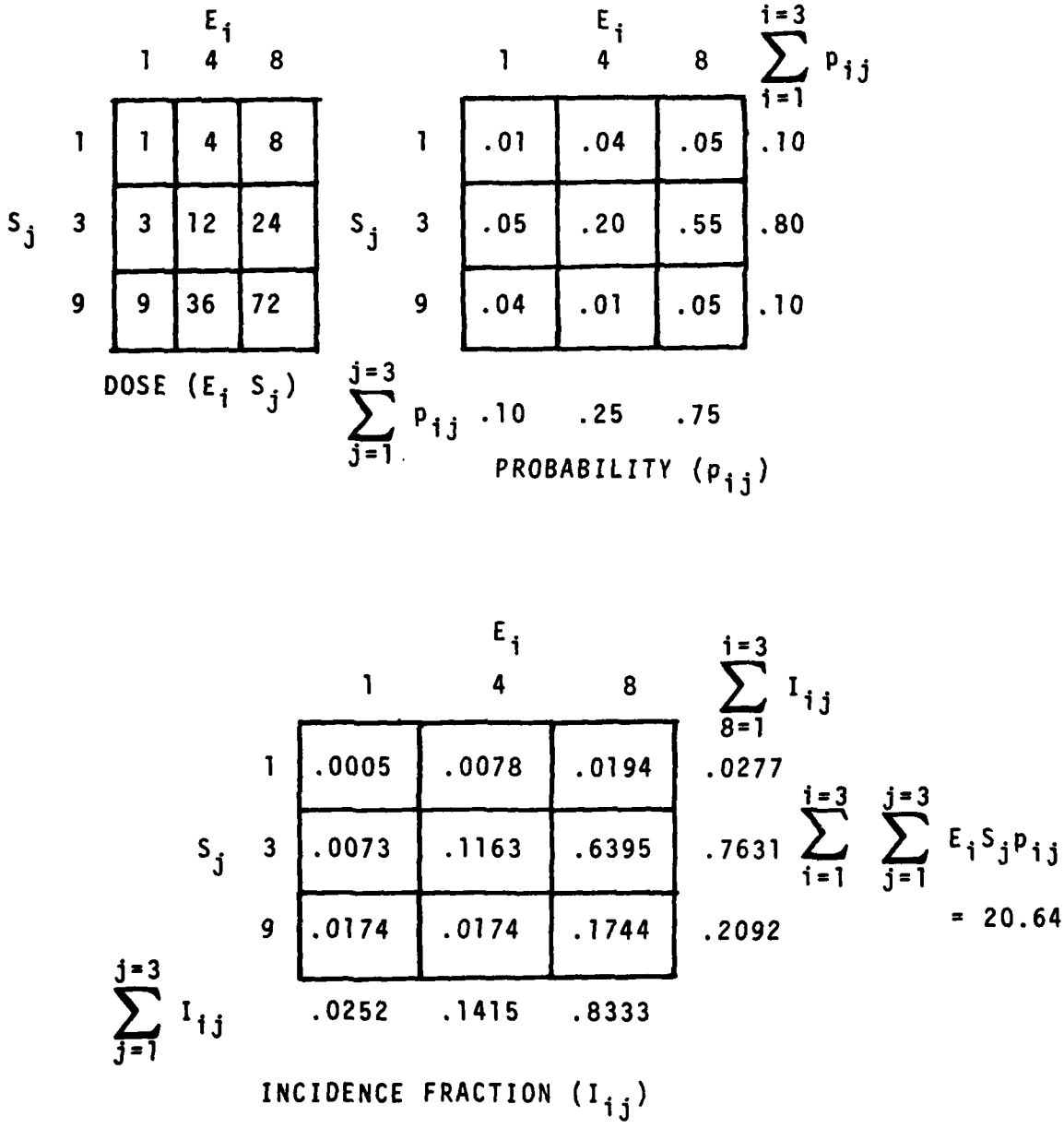

FIGURE 8. DOSE, PROBABILITY, AND INCIDENCE MATRICES FOR A RURAL HYPOTHETICAL EXAMPLE WITH A NEW YORK CITY SENSITIVITY DISTRIBUTION

assumed order of magnitude increase in the high exposure-moderate sensitivity population fraction where the majority (64 percent) of rural skin cancers are found.

TABLE 7. POPULATION AND INCIDENCE PERCENTAGES FOR A HYPOTHETICAL RURAL REGION WITH A NEW YORK CITY SENSITIVITY DISTRIBUTION

	EXPOSURE		SENSITIVITY	
LEVEL	POPULATION	INCIDENCE	POPULATION	INCIDENCE
Low	10	2.5	10	2.8
Moderate	25	14.2	80	76.3
High	65	83.3	10	20.9

The ratio of skin cancer incidence of this rural example to the incidence for New York City is equal to the ratio of the respective denominators of Eq. (24), which is equal to 20.64/8.5194 or 2.42.

In Fig. 9 the effect of a sensitivity distribution change has been investigated in which the fraction of the high sensitivity group assumed in Figs. 7 and 8 is doubled from 0.1 to 0.2. This increase is assumed to be associated with a corresponding decrease in the moderate sensitivity group and no change in the low sensitivity group, i.e., $f_1 = 0.1$, $f_2 = 0.7$, and $f_3 = 0.20$. A comparison of the population and incidence percentages for this rural case is given in Table 8. The percentages by level of exposure remained essentially unchanged from the percentages in Table 7. The fraction of the incidence contributed by the high sensitivity group is almost double the population fraction of 20 percent. However, because 70 percent of the population falls in the moderate sensitivity group, the total incidence for the case in Fig. 9 increased by a factor of only 23.7/20.64, or 1.15 over the case in Fig. 8.

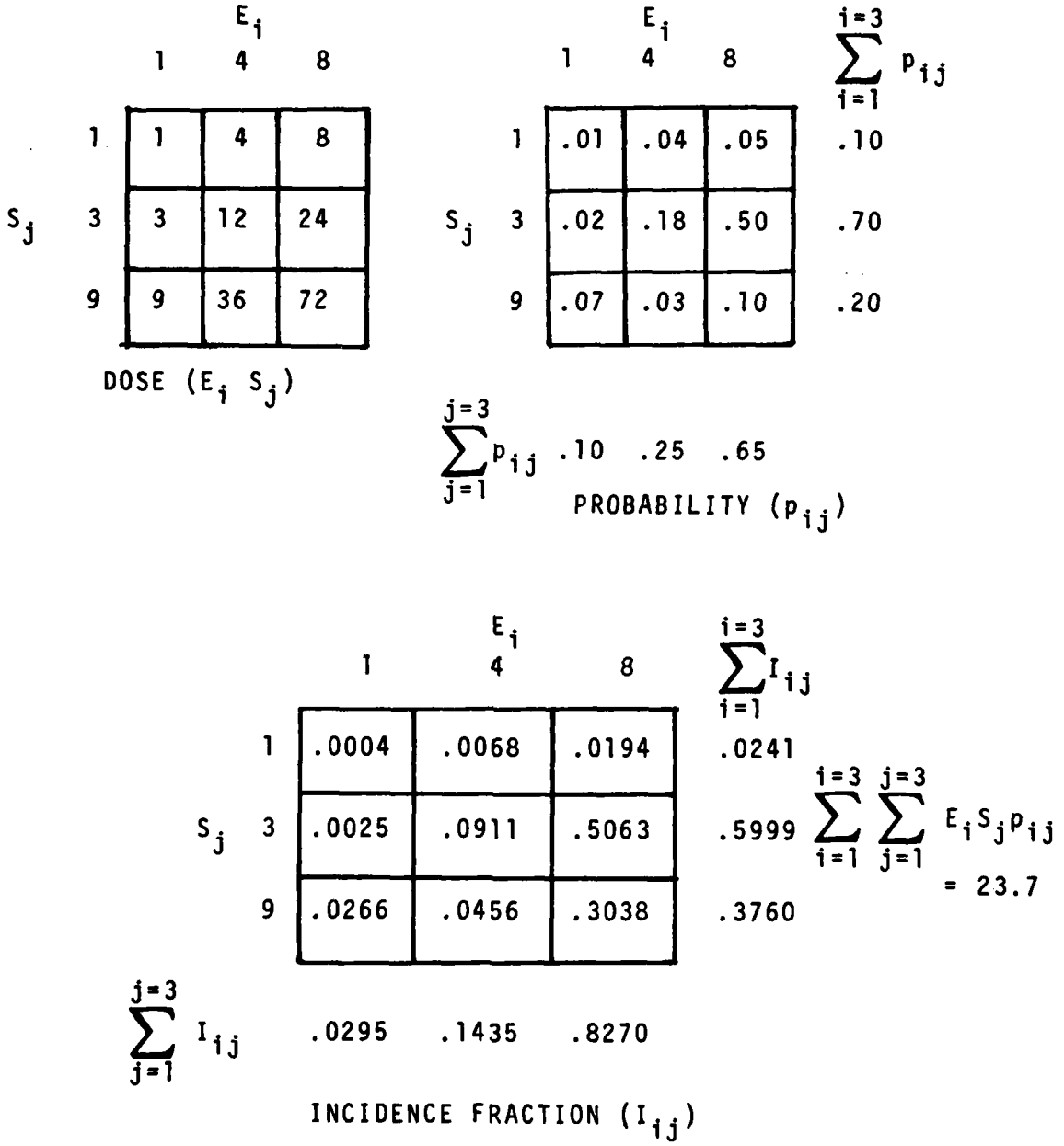

FIGURE 9. DOSE, PROBABILITY, AND INCIDENCE MATRICES FOR A RURAL HYPOTHETICAL EXAMPLE WITH $f_1 = 0.1$ and $f_3 = 0.2$

TABLE 8. POPULATION AND INCIDENCE PERCENTAGES FOR A HYPOTHETICAL RURAL REGION WITH $f_1 = 0.1$ and $f_3 = 0.2$

	EXPOSURE		SENSITIVITY	
LEVEL	POPULATION	INCIDENCE	POPULATION	INCIDENCE
Low	10	3.0	10	2.4
Moderate	25	14.3	70	60.0
High	65	82.7	20	37.6

V. EFFECT OF SENSITIVITY DISTRIBUTION ON SKIN CANCER INCIDENCE

It should not be inferred from the above example that differential sensitivity is not a very significant parameter in skin cancer incidence. To illustrate the large effect that the sensitivity distribution can have, consider the case of populations of equal exposure and variable values of f_1 and f_3. These two values define the sensitivity distribution for a population divided into 3 sensitivity groups since $f_2 = 1 - f_1 - f_3$. The incidence for a given sensitivity distribution is

$$I = k \left[S_1 f_1 + S_2 f_2 + S_3 f_3 \right] , \qquad (25)$$

where k is a constant whose value is dependent on exposure. However, it is the relative incidence I' or I/k that is of interest here. Assuming the sensitivity values $S_1 = 1$, $S_2 = 3$, and $S_3 = 9$ of Case H,

$$I' = f_1 + 3 f_2 + 9 f_3 \qquad (26)$$

$$= 3 - 2 f_1 + 6 f_3 \quad . \qquad (27)$$

I' is plotted vs f_3 in Fig. 10, with f_1 as a parameter. For a given value of f_1, the value of f_3 is constrained by the inequality

$$0 \leq f_3 \leq 1 - f_1 \quad . \qquad (28)$$

Note that for a population with a sensitivity distribution $f_1 = 0.1$, $f_3 = 0.6$ as might be characteristic of a population

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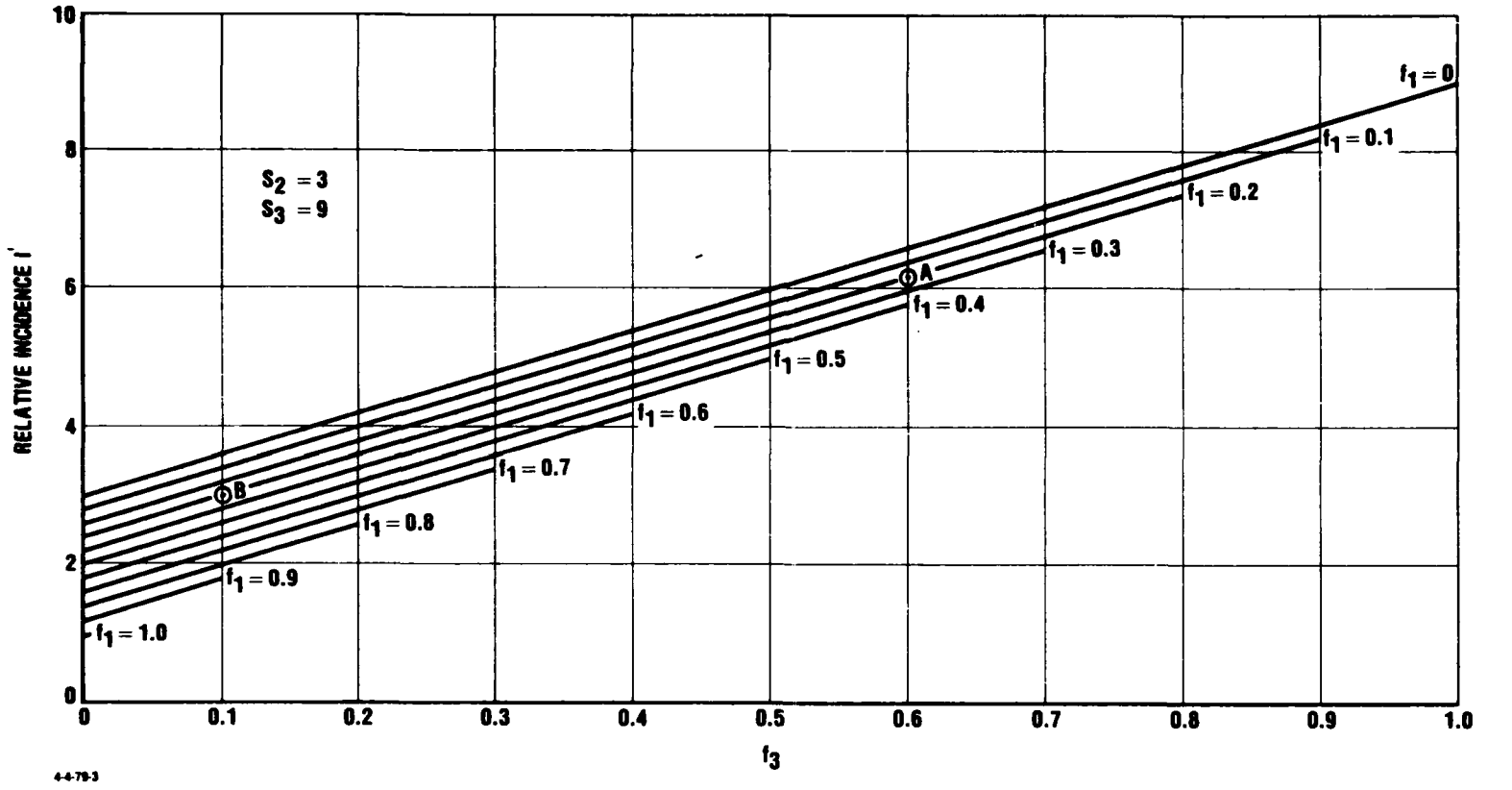

FIGURE 10. Relative incidence for equal exposure populations vs sensitivity distribution.

dominated by residents of Scandinavian or Irish descent, $I' = 6.2$ (point A in Fig. 10); for a population with a distribution $f_1 = 0.3$, $f_3 = 0.1$, as might be characteristic of a population with many residents of Mediterranean descent and few of Scandinavian or Irish, $I' = 3.0$ (point B in Fig. 10). When a possible factor of 2 or more in incidence due to the effects of differential sensitivity is combined with a possible factor of 2 or more due to the effects of differential exposure, it is not too surprising that a factor of 4 or more in incidence could be registered in different populations at the same latitude, as illustrated by the data in Fig. 1.

VI. EFFECTS OF NON-SOLAR-INDUCED SKIN CANCER INCIDENCE

A substantial fraction of basal cell epitheliomas, perhaps 50 percent in northern U.S. cities (Ref. 1), are not induced by solar ultraviolet radiation. Inclusion of such cancers in mathematical models can lead to significant errors, particularly when comparing incidences in different regions to determine the biological amplification factor. This effect is easily illustrated by making a one-dimensional incidence comparison between two regions, i.e., the sensitivity of the populations are assumed to be equal, but aggregate exposure is represented by UV-B dose D_A in region A and D_B in region B.

If all skin cancers reported are assumed to be induced by solar ultraviolet radiation, the incidences in regions A and B would be incorrectly represented by the relations

$$I_A = k\, D_A^{n_o} \tag{29}$$

$$I_B = k\, D_B^{n_o} , \tag{30}$$

where k is a constant and n_o is the biological amplification factor, calculated on the basis of the erroneous assumption. Solving Eqs. (29) and (30) for n_o,

$$n_o = \frac{\ell n\left(\frac{I_A}{I_B}\right)}{\ell n\left(\frac{D_B}{D_A}\right)} . \tag{31}$$

Since there is an incidence I_{XA} of non-solar-induced skin cancer in region A and an incidence I_{XB} of non-solar-induced skin cancer in region B,

$$I_A = k\, D_A^{n_s} + I_{XA} \tag{32}$$

$$I_B = k\, D_B^{n_s} + I_{XB}\ , \tag{33}$$

where n_s is the amplification factor for solar-induced skin cancers only. Solving Eqs. (32) and (33) for n_s,

$$n_s = \frac{\ell n\left(\frac{I_A - I_{XA}}{I_B - I_{XB}}\right)}{\ell n\left(\frac{D_B}{D_A}\right)}\ . \tag{34}$$

The error in biological amplification can be expressed by the ratio n_s/n_o or, from Eqs. (31) and (34),

$$\frac{n_s}{n_o} = \frac{\ell n\left(\frac{I_A - I_{XA}}{I_B - I_{XB}}\right)}{\ell n\left(\frac{I_A}{I_B}\right)}\ . \tag{35}$$

In Fib. 11, the ratio n_s/n_o is plotted vs the non-solar induced skin cancer incidence I_{XB} for region B, for the Case I_A = 200 and I_{XA} = 20 or 10 percent of I_A. Three cases for I_B are shown in Fig. 11: I_B = 50, 100, and 150. The values of I_{XB} for each case were assumed to lie between zero and 0.5 I_B. The case $n_s = n_o$ can only occur when the fraction of non-solar-induced skin cases is the same in regions A and B, or

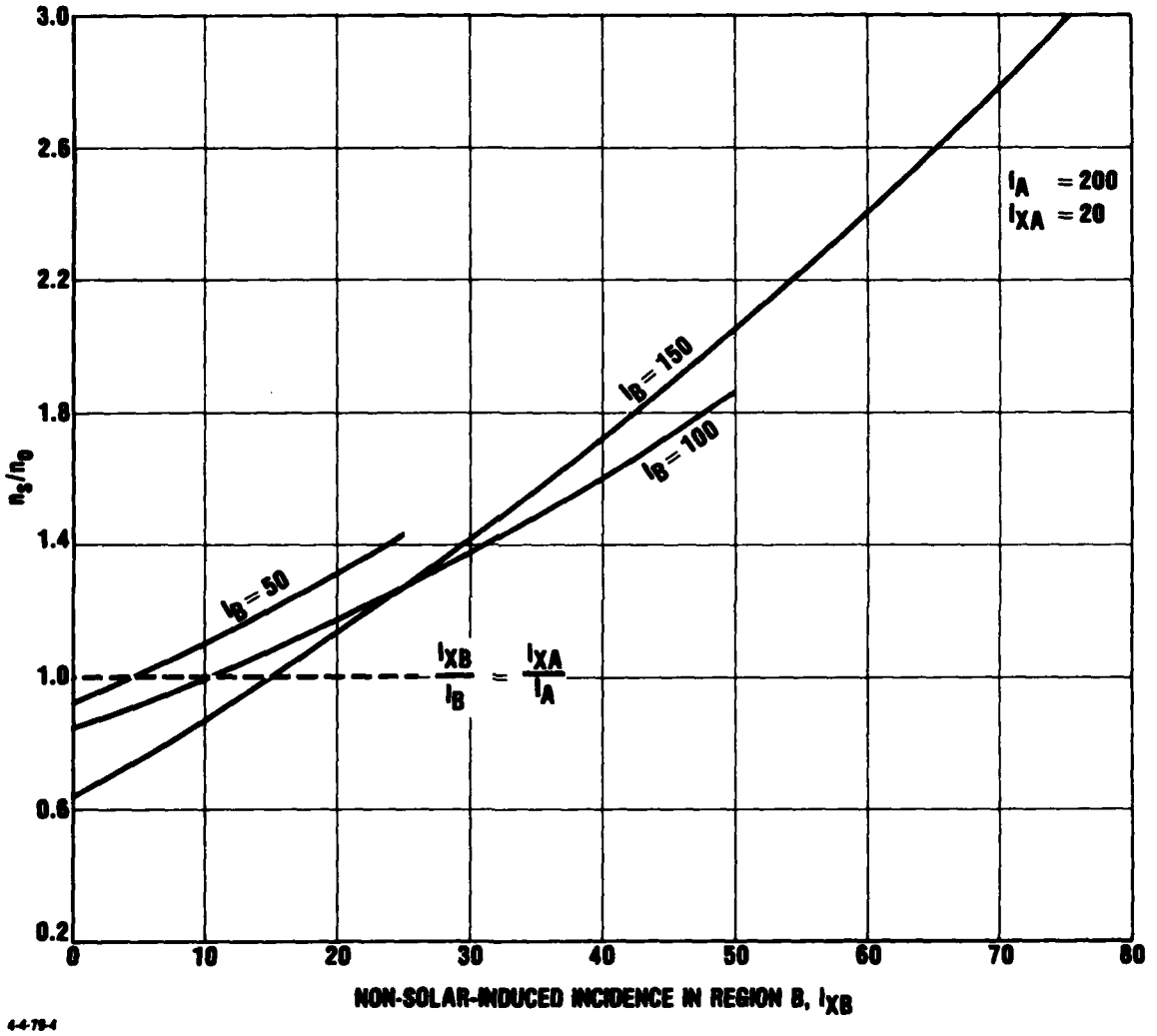

FIGURE 11. Effect of non-solar-induced skin cancer incidence on biological amplification factor.

$$\frac{I_{XB}}{I_B} = \frac{I_{XA}}{I_A} \quad . \tag{36}$$

However, it can be expected that in general the region of significantly higher incidence (region A) will have associated with it a smaller fraction of non-solar induced skin cancers, so that

$$\frac{I_{XB}}{I_B} > \frac{I_{XA}}{I_A} \quad . \tag{37}$$

and it would follow that

$$n_s > n_o \quad . \tag{38}$$

If $I_{XB} = I_{XA} = 20$, the error in n_s with respect to n_o lies between 14 percent ($I_B = 150$) and 30 percent ($I_B = 50$). If $I_{XB} = 40$, the error in n_s is 60 percent for $I_B = 100$, and 72 percent for $I_B = 150$.

If the incorrect biological amplification factor is used to predict the expected number N of additional skin cancer cases that would result in some geographic region as a result of a hypothetical increase in ultraviolet dose ΔD following a reduction in the thickness of the stratospheric ozone layer, there will be an error in N. If P is the population of the region, the additional number of skin cancers ΔN_o based on the use of biological amplification factor n_o is

$$\Delta N_o = P\ I\ n_o \left(\frac{\Delta D}{D}\right) \quad . \tag{39}$$

The correct amplification factor n_s, however, should only be applied to the solar-related cases of skin cancer, or

$$\Delta N = P\ (I - I_X)\ n_s \left(\frac{\Delta D}{D}\right) \quad . \tag{40}$$

The error in N may be represented by the ratio $\Delta N/\Delta N_o$ or

$$\frac{\Delta N}{\Delta N_o} = \left(1 - \frac{I_X}{I}\right)\left(\frac{n_s}{n_o}\right) \quad . \tag{41}$$

In Fig. 12, the ratio $\Delta N/\Delta N_o$ is plotted vs n_s/n_o with the non-solar-related skin cancer incidence I_X as a parameter. The error in N may be positive or negative. If $I_X < (1-n_o/n_s)\ I$, then $\Delta N > \Delta N_o$ and the expected number of additional cases would be underestimated by ΔN_o; if $I_X > (1 - n_o/n_s)\ I$, then $\Delta N < \Delta N_o$ and the number of additional cases would be overestimated.

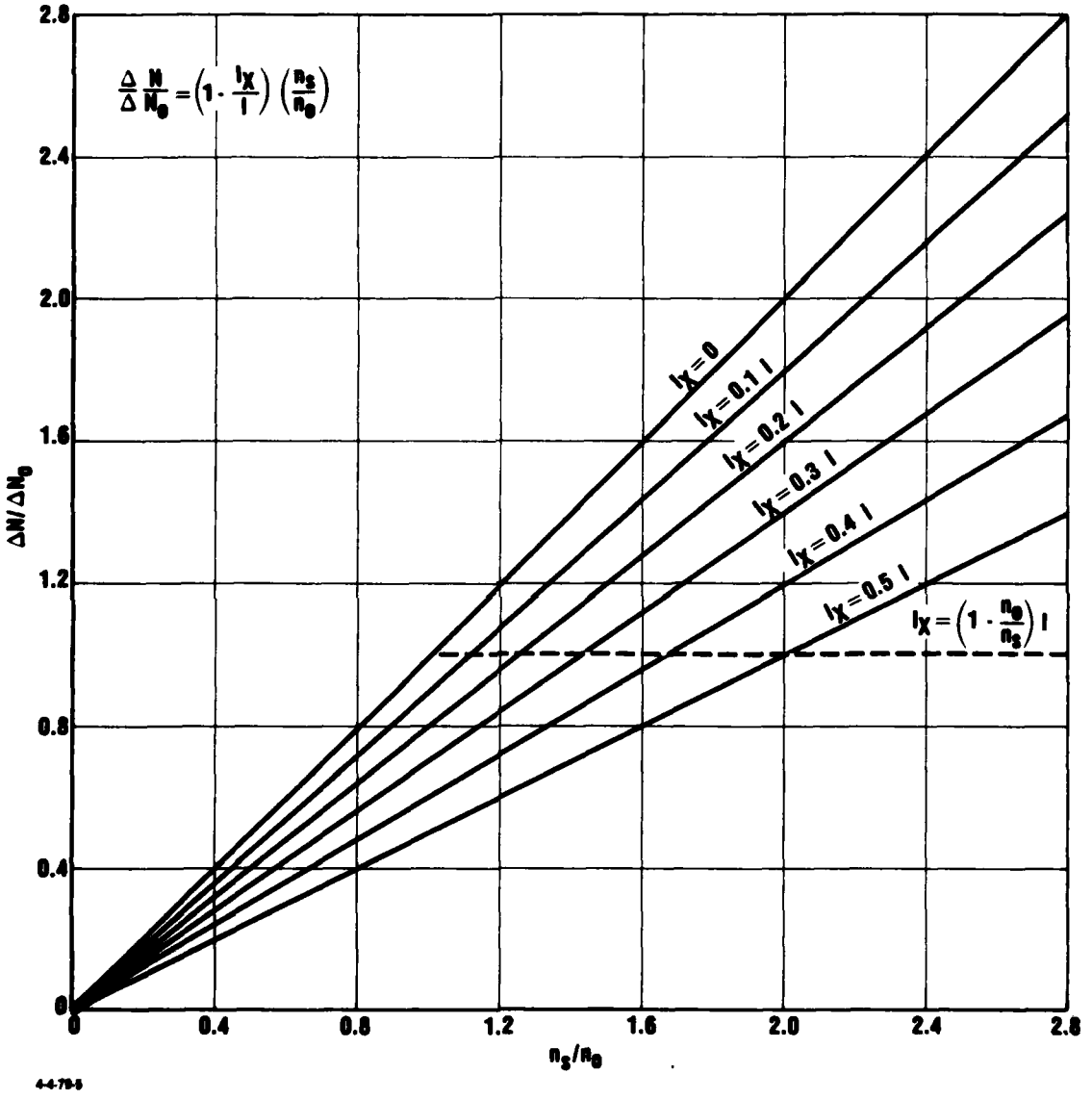

FIGURE 12. Effect of non-solar-induced skin cancers on number of predicted additional skin cancers in a geographic region.

VII. MODELLING NON-MELANOMA SKIN CANCER INCIDENCE BY TYPE OF TUMOR AND SEX

The incidence of skin cancer varies not only with age, exposure, and sensitivity, but also by type of tumor and sex. The total non-melanoma skin cancer incidence I is the sex weighted sum of six incidence terms, i.e.,

$$I = M\,(I_{bm} + I_{sm} + I_{xm}) + (1 - M)(I_{bf} + I_{sf} + I_{xf}) \quad (42)$$

where M is the fraction of adult males, subscripts m and f denote male and female, respectively, subscripts b and s denote basal cell epitheliomas and squamous cell carcinomas, respectively, and subscript x denotes non-solar-related carcinomas. Each of the four solar-related skin cancer incidence terms of interest is composed of the sum of the incidences of each anatomic site which vary in frequency with geographic region (Ref. 1). The age-specific incidence of basal cell epithelioma differs from that of squamous cell carcinoma (Ref. 6), and the dose-response relationship could therefore also be expected to differ for these two types of tumors. Adding further to the complexity of the skin cancer modelling problem is the likelihood that temperature, humidity, and wind speed affect skin cancer incidence (Ref. 1). It is therefore apparent that a skin cancer model, including differential exposure and differential sensitivity, while much more sophisticated than an aggregate model, represents but a first step in a comprehensive quantitative understanding of the epidemiology of non-melanoma skin cancer.

VIII. EFFECTS OF CHANGES IN STRATOSPHERIC OZONE

Most recent analyses of aircraft atmospheric pollution indicate that "the NO_x constituent of engine exhaust from both SSTs at 17 to 20 km (except in very large numbers) and from subsonics at 9 to 14 km, will contribute to an increase in the ozone column; water vapor emissions, on the other hand, at least from SSTs, (will) tend to decrease ozone unless, as some modeling results indicate, radiative feedback attempts compensate. The net effect on the ozone column, of water and NO_x emissions, with current NO_x emission indices, is apparently slightly positive for both classes of aircraft in foreseeable numbers" (Ref. 7).

Halocarbons in the stratosphere will probably decrease ozone more than aircraft will increase ozone. Halocarbon effects and aircraft effects (and all others) will change with time. Time-dependent modelling results showing both effects are not available: a brief review of the current literature suggests halocarbon effects will dominate. However, stratospheric ozone changes also may be caused by climatic as well as chemical changes (Ref. 8). For purposes of discussion, the effects of a postulated increase in stratospheric ozone also deserve some consideration.

The magnitude of a decrease in solar UV radiation due to a postulated increase in total ozone was discussed in Ref. 9. The relationship is symmetrical, i.e., if a small specified percentage decrease in ozone leads to a factor K increase in ultraviolet exposure E or ultraviolet dose D, an increase in ozone of the same percentage leads to a factor K^{-1} decrease in D. For a small percentage decrease in D, the fractional decrease in skin cancer incidence $\Delta I/I$ is given by $n\ \Delta D/D$. The skin cancer

mathematical model itself is, of course, unaffected by the direction of the change in the input parameter. The biological consequences of a thicker ozone layer are another matter. Although skin cancer incidence would decrease -- an obvious benefit to society -- the healthful effects of solar ultraviolet radiation would also be reduced. These healthful effects include prevention of rickets and beneficial skin effects which do not readily lend themselves to quantification. Among these are skin conditions such as psoriasis, sebhorric dermatitis, acne, and actopic exema, conditions in which all practicing dermatologists note an improvement of the skin during the summer months when exposure to solar radiation is increased.*

*Personal communication with Dr. T. P. Nigra, Chairman, Dermatology Section, Washington Hospital Center.

IX. IMPLICATIONS OF MODEL RESULTS TO PREDICTION OF INCREASE IN SKIN CANCER INCIDENCE

The technique most widely used to predict the increase in skin cancer incidence resulting from a hypothetical decrease in the thickness of the stratospheric ozone layer is to compare incidence values for geographic regions of different latitude with calculated values of the corresponding UV-B dose incident on the ground (e.g., Ref. 10). Arbitrary adjustment is made for aggregate population exposure differences due to differences in length of season and climate, an adjustment which was unnecessary in the comparisons investigated in this paper because New York City and Iowa are at approximately the same latitude. The results of the model illustrate that a refinement of this technique should include the important effects of differential exposure and differential sensitivity within the population of each of the geographic regions used for comparison purposes. Clearly, such a refinement is difficult if not impossible to implement with the present lack of knowledge of the distribution of population exposure and the distribution of sensitivity in any given geographic region. It is to be hoped that, sometime in the near future, there will exist a data bank of population exposure distributions based on surveys with personal DUV dosimeter readings (such dosimeters are currently in research and development*). There already exists a DUV network which is providing information on the daily DUV dose incident on the ground

*One such personal dosimeter is currently under development by Ricker Laboratories Inc., St. Paul, Minnesota.

for each day of the year (Ref. 11). There are also dermatologists investigating the difficult problem of finding a suitable measure of individual sensitivity to skin cancer based on characteristics of the skin, e.g., time to show a minimal erythemal dose*. A complicating factor is the effect of tanning and pigmentation. Long-term exposure to sunlight produces tanning in some individuals and thereby reduces their sensitivity to light. An additional approach could be genetic predisposition to skin cancer. Techniques are at hand to genetically type individuals with regard to their HLA, B, C, and D loci (tissue typing used in transplant immunology)**. If a sensitivity measure can be found and, with more detailed and accurate epidemiological data than are now available, demonstrated to be satisfactorily correlated with skin cancer incidence, the necessary foundations will have been laid for the inclusion of differential exposure and differential sensitivity into a model predicting increases in skin cancer incidence that would follow a stratospheric ozone reduction. Such a model should incorporate the methodology outlined in this paper, but the number of exposure-sensitivity groups should probably be increased from 9 to 16 or more.

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* Such as the Wucherpfennig method of measuring minimum erythemal dose which consists of spatially filtered wheels providing varying levels of exposure (described at a meeting sponsored by the Association Internationale de Photobiologie in Lausanne, Switzerland, September 26-29, 1978).

** Personal Communication with Dr. T. P. Nigra, Chairman, Dermatology Section, Washington Hospital Center.

X. CONCLUSIONS

The principal conclusions that can be drawn from the analysis in this paper are the following:

1. Differential exposure and differential sensitivity in a population have a significant impact on skin cancer incidence, and should be taken into consideration when comparing skin cancer incidence in populations residing in different geographic regions.
2. It is possible to mathematically model skin cancer incidence, including the effects of differential exposure and differential sensitivity.
3. Parameters identified as essential to the formulation of a mathematical model are the following:
    a. The range of exposure values E_i.
    b. The probability density function of exposure $p(E_i)$.
    c. The range of sensitivity values S_i.
    d. The probability density function of sensitivity $p(S_i)$ or f_i.
    e. The biological amplification factor n.
4. A mathematical model of skin cancer incidence based on a division of the population into three exposure and three sensitivity groups was derived and applied to the case of New York City. A set of 22 cases was investigated. Exposure and sensitivity values which appear to best fit the input incidence data were determined by eliminating

those cases which led to negative probabilities. The remaining solutions were then subjected to criteria designed to minimize departures from expected behavior. Of the cases investigated, the best New York City solution had the following set of values: $n = 1$, $E_1 = 1$, $E_2 = 4$, $E_3 = 8$, $S_1 = 1$, $S_2 = 3$, $S_3 = 9$, and $f_1 = f_3 = 0.1$.

5. A reversal of the New York City population exposure distribution was assumed for a rural region such as Iowa, assuming no change in the population sensitivity distribution. It was found that Iowa could have more than double the incidence of New York City under the assumed conditions.

6. Two white populations with markedly different sensitivity distributions and equal exposure could have incidences that differ by a factor of 2 or more.

7. The effect of not eliminating non-solar-related skin cancers in skin cancer incidence data on the prediction of increased incidence due to stratospheric ozone reduction is to introduce an error which may be positive or negative.

8. In order to effectively utilize the mathematical model derived in this paper for predicting skin cancer increases resulting from stratospheric ozone depletion, it will be necessary to pursue the following programs:

    a. Develop a personal UV-B dosimeter (in progress).

    b. Conduct exposure surveys of individuals wearing a personal UV-B dosimeter in various population

groups residing in various geographic regions* for which accurate skin cancer incidence data is available.

c. Determine a measure of sensitivity to skin cancer which can be correlated to incidence and which is easily applied in the field (under investigation**).

d. Classify various population groups residing in various geographic regions for which skin cancer incidence data is available according to (c).

e. Pathology criteria are needed to distinguish skin cancers that are caused by solar ultraviolet radiation from those that are not.

f. Non-melanoma skin cancer incidence is currently reported to cancer registries by age and sex. It should also be reported by type of tumor (basal cell epithelioma and squamous cell carcinoma), by relation to solar ultraviolet radiation, if and when item (e) above becomes feasible, and by sensitivity, if and when item (c) becomes feasible.

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*In England, for example, Dr. I. Magnus has reported (Lausanne, Switzerland, Sept. 1978) that tests with his personal UV badges indicate that sendentary people receive approximately three percent of the ambient DUV radiation.

**Dr. J. C. Van der Leun has suggested (Lausanne, Switzerland, Sept. 1978) measures of carcinogenesis susceptibility other than minimum erythemal dose such as increase in redness with increase in dose, and an erythema index which measures the increase in the size of the red area with an increase in dose.

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